Decision Memo for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications (CAG-00383N)

Decision Summary

Emerging safety concerns (thrombosis, cardiovascular events, tumor progression, and reduced survival) derived from clinical trials in several cancer and non-cancer populations prompted CMS to review its coverage of erythropoiesis stimulating agents (ESAs). We reviewed a large volume of scientific literature, including basic science research, to see if these safety signals seen in randomized controlled trials could be reasonably explained in whole or in part by the actions of ESAs on normal or cancerous cells. In doing so we proposed conditions of coverage based on expression of erythropoietin receptors. The scientific understanding of this mechanism is a subject of continuing debate among stakeholders, continues to evolve, and can only be resolved through additional studies. We also reviewed a large volume of comments on the use of ESAs in myelodysplastic syndrome (MDS), a pre-malignant syndrome that transforms into acute myeloid leukemia (AML) in many patients. Though we continue to be interested in these specific issues, this final decision does not differentiate ESA coverage by the erythropoietin receptor status of the underlying disease, and we have narrowed the scope of this final decision to make no national coverage determination (NCD) at this time on the use of ESAs in MDS.

CMS has determined that there is sufficient evidence to conclude that erythropoiesis stimulating agent (ESA) treatment is not reasonable and necessary for beneficiaries with certain clinical conditions, either because of a deleterious effect of the ESA on their underlying disease or because the underlying disease increases their risk of adverse effects related to ESA use. These conditions include:

1. any anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis;
2. the anemia associated with the treatment of acute and chronic myelogenous leukemias (CML, AML), or erythroid cancers;
3. the anemia of cancer not related to cancer treatment;
4. any anemia associated only with radiotherapy;
5. prophylactic use to prevent chemotherapy-induced anemia;
6. prophylactic use to reduce tumor hypoxia;
7. patients with erythropoietin-type resistance due to neutralizing antibodies; and
8. anemia due to cancer treatment if patients have uncontrolled hypertension.

We have also determined that ESA treatment for the anemia secondary to myelosuppressive anticancer chemotherapy in solid tumors, multiple myeloma, lymphoma and lymphocytic leukemia is only reasonable and necessary under the following specified conditions:

1. The hemoglobin level immediately prior to initiation or maintenance of ESA treatment is < 10 g/dL (or the hematocrit is < 30%).
2. The starting dose for ESA treatment is the recommended FDA label starting dose, no more than 150 U/kg/three times weekly for epoetin and 2.25 mcg/kg/weekly for darbepoetin alpha. Equivalent doses may be given over other approved time periods.

3. Maintenance of ESA therapy is the starting dose if the hemoglobin level remains below 10 g/dL (or hematocrit is < 30%) 4 weeks after initiation of therapy and the rise in hemoglobin is ≥ 1g/dL (hematocrit ≥ 3%).
4. For patients whose hemoglobin rises <1 g/dl (hematocrit rise <3%) compared to pretreatment baseline over 4 weeks of treatment and whose hemoglobin level remains <10 g/dL after the 4 weeks of treatment (or the hematocrit is <30%), the recommended FDA label starting dose may be increased once by 25%. Continued use of the drug is not reasonable and necessary if the hemoglobin rises <1 g/dl (hematocrit rise <3 %) compared to pretreatment baseline by 8 weeks of treatment.
5. Continued administration of the drug is not reasonable and necessary if there is a rapid rise in hemoglobin > 1 g/dl (hematocrit > 3%) over 2 weeks of treatment unless the hemoglobin remains below or subsequently falls to < 10 g/dL (or the hematocrit is < 30%). Continuation and reinstitution of ESA therapy must include a dose reduction of 25% from the previously administered dose.
6. ESA treatment duration for each course of chemotherapy includes the 8 weeks following the final dose of myelosuppressive chemotherapy in a chemotherapy regimen.

Local Medicare contractors may continue to make reasonable and necessary determinations on all uses of ESAs that are not determined by NCD.

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Decision Memo

TO: Administrative File: CAG #000383N
The Use of Erythropoiesis Stimulating Agents in Cancer and Related Neoplastic Conditions

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SUBJECT: Coverage Decision Memorandum for the Use of Erythropoiesis Stimulating Agents in Cancer and Related Neoplastic Conditions

DATE: July 30, 2007

I. Decision

Emerging safety concerns (thrombosis, cardiovascular events, tumor progression, and reduced survival) derived from clinical trials in several cancer and non-cancer populations prompted CMS to review its coverage of erythropoiesis stimulating agents (ESAs). We reviewed a large volume of scientific literature, including basic science research, to see if these safety signals seen in randomized controlled trials could be reasonably explained in whole or in part by the actions of ESAs on normal or cancerous cells. In doing so we proposed conditions of coverage based on expression of erythropoietin receptors. The scientific understanding of this mechanism is a subject of continuing debate among stakeholders, continues to evolve, and can only be resolved through additional studies. We also reviewed a large volume of comments on the use of ESAs in myelodysplastic syndrome (MDS), a pre-malignant syndrome that transforms into acute myeloid leukemia (AML) in many patients. Though we continue to be interested in these specific issues, this final decision does not differentiate ESA coverage by the erythropoietin receptor status of the underlying disease, and we have narrowed the scope of this final decision to make no national coverage determination (NCD) at this time on the use of ESAs in MDS.

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6. ESA treatment duration for each course of chemotherapy includes the 8 weeks following the final dose of myelosuppressive chemotherapy in a chemotherapy regimen.

Local Medicare contractors may continue to make reasonable and necessary determinations on all uses of ESAs that are not determined by NCD.

II. Background

In this section in our proposed decision memorandum, we described the technological developments that gave rise to the use of genetically engineered (recombinant) erythropoietin and related ESAs (see appendix A). We then described the anemias for which ESAs are prescribed in oncologic conditions, with an emphasis on solid tumors that constituted the majority of tumors in the studies upon which FDA approval was based. We refer the reader to Appendix A for a detailed discussion of the biochemical background of ESAs and their current usages. We will summarize these points here.

Erythropoietin is a glycoprotein produced primarily in the kidney and to a lesser extent in the liver. In the classic hormone pathway, erythropoietin regulates erythrocyte production by stimulating red cell production in the bone marrow. Suppression of erythropoietin production or suppression of the bone marrow response to erythropoietin has resulted in anemias in several disease processes to include renal disease, cancer treatment, other chronic diseases and use of certain drugs.

To combat these anemias, several forms of recombinant human erythropoietin have been developed. The two currently available in the US are epoetin and darbepoetin alpha. Recombinant erythropoietin was initially used as a replacement for missing hormone in select patients with anemia of end-stage renal disease. Use of ESAs has been extended to a variety of anemic conditions including the anemia of chronic renal disease (not yet on dialysis), anemia secondary to chemotherapy of solid tumors, anemia secondary to AZT therapy, anemia in myelodysplastic disorders and prophylactic use during the perioperative period to reduce the need for allogenic blood transfusions.

In cancer, anemia occurs with varying degrees of frequency and severity. It is most frequent in genitourinary, gynecologic, lung, and hematologic malignancies. Anemia may be directly related to cancer type or to its treatment.

Oncologic anemia occurs by a variety of mechanisms. Poor oral intake or altered metabolism may reduce nutrients (folate, iron, vitamin B-12) essential for the red cell production. Antibodies in certain tumor types may cause increased erythrocyte destruction through hemolysis. Tumors may cause blood loss via tissue invasion, e.g. gastrointestinal bleeding from colon cancer. Other neoplasms, particularly hematologic malignancies (leukemia, lymphoma, multiple myeloma) can invade the bone marrow and disrupt the erythropoietic microenvironment. In more advanced cases, there may be marrow replacement with tumor or amyloid. Marrow dysfunction can occur, however, even in the absence of frank invasion (Faquin 1992; Mikami 1998). Inflammatory proteins from interactions between the immune system and tumor cells are thought to cause inappropriately low erythropoietin production and poor iron utilization as well as a direct suppression of red cell production.

The treatment of cancer may also cause anemia. Radical cancer surgery can result in acute blood loss. Radiotherapy and many cytotoxic chemotherapeutic agents cause marrow suppression to some degree. Damage is due to a variety of mechanisms. For example, alkylating agents cause cumulative DNA damage, anti-metabolites damage DNA indirectly, and platinum-containing agents appear to damage erythropoietin-producing renal tubule cells.

Myelodysplastic disorders are a heterogenous group of pre-leukemic diseases characterized by cytopenias due to abnormal hematopoietic differentiation and maturation. The disease may be idiopathic or secondary to chemotherapy or radiation therapy for other disease. The primary defect resides in hematopoietic stem cells. New cases exceed 10,000/year. Transformation to acute non-lymphocytic leukemia occurs in 10 to 40% of patients with idiopathic MDS. Thrombocytopenic bleeding and neutropenic infections contribute to death. Survival at 3 years is approximately 40% for those over 50 (Ma 2007). Transfusion dependence and risk for leukemic transformation appear related to disease severity/diagnostic category. Therapeutic treatment of MDS related anemia requires treatment of the underlying marrow disorder. Treatment in younger patients is allogenic bone marrow transplantation. Treatment with cytotoxic agents has demonstrated limited utility. Supportive care includes transfusions and avoidance/treatment of iron overload. Readers interested in more information may wish to review the discussion of MDS by the National Cancer Institute (NCI) at *http://www.cancer.gov/cancertopics*.

In opening this NCD in March of this year, CMS stated that it would be reviewing the non-ESRD uses of ESAs. In our proposed decision in May of this year, we restricted our proposal to oncologic uses of ESAs. However, as pointed out to us, MDS is not an oncologic condition. Thus, we are making no decision on MDS in this final decision.

The level at which anemia requires intervention is not well established. By tradition, patients have been transfused at the hemoglobin level of 7 or 8 g/dl to avoid symptoms and physiologic complications. A transfusion of 2 or more units would result in an increase of at least 2 g/dl of hemoglobin (6 units of hematocrit). Indeed, one of the endpoints for pharmaceutical registration, need for transfusion, employed an 8 g/dl hemoglobin cut-off (FDA Medical Officer Review, Aranesp 2002). Most of these practices, however, are based on empiric observations and not clinical trials. In one of the few studies, Carson et al. found that hip-fracture patients transfused to hemoglobin levels in excess of 10 g/dl did not have more exercise tolerance than non-transfused patients who were transfused after hemoglobin levels dropped to below 8 g/dl or patients became symptomatic (Carson 1998).

The British Blood Transfusion Society has delineated the weaknesses in our knowledge base. Their guidelines state that transfusions are indicated in patients with hemoglobin levels less than 7 g/dl and that transfusion should not be undertaken for hemoglobin levels greater than 10 g/dl. They indicate that management of patients with hemoglobin levels between 7 and 10 remains unclear although the hemoglobin threshold for the treatment of patients with co-morbid conditions is probably higher than 7 g/dl. Although they have done so in the past, the College of American Pathologists (CAP) no longer issues transfusion practice guidelines.

Other groups have developed definitions for anemia and have been cited for these definitions, but these definitions cannot be extrapolated into guidelines for oncologic treatment. The World Health Organization (WHO) definitions for anemia were developed for surveillance of anemia due to nutritional deficiency and parasitic infections. The National Cancer Institute (NCI) has information on anemia, but does not issue treatment guidelines (Robin Bason 301-594-9051; NCI anemia information from web). Both the NCI and WHO consider hemoglobin levels less than 6.5 g/dl to be life-threatening.

III. History of Medicare Coverage

Prior to this National Coverage Analysis, there was no National Coverage Decision (NCD) concerning the use of ESAs for the indications discussed in this Decision Memorandum. Currently, the Medicare benefit for ESAs for end-stage renal disease (ESRD) related anemia is outlined in the Medicare Benefit Policy Manual, Chapter 11, Section 90 and Chapter 15, Section 50.5.2. For other indications, Medicare coverage of ESAs administered incident to a physician service for other indications under Part B is determined by local Medicare contractors.

Medicare is a defined benefit program. An item or service must fall within a benefit category as a prerequisite to Medicare coverage. § 1812 (Scope of Part A); § 1832 (Scope of Part B); § 1861(s) (Definition of Medical and Other Health Services). ESAs fall within the benefit categories specified in 1861(s)(2)(A) & 1861(s)(2)(B) of the Social Security Act.

IV. Timeline of Recent Activities

March 14, 2007	CMS opened an internally generated National Coverage Decision (NCD) to evaluate coverage of uses of ESAs in non-renal disease applications. The initial 30-day comment period opened.
April 13, 2007	The initial public comment period closed; 69 timely comments were received.
May 14, 2007	CMS published the Proposed Decision Memorandum. The 30-day public comment period opened.
June 13, 2007	The public comment period on the proposed decision closed. 2641 timely comments were received.

V. FDA Status

A. Erythropoietin-alpha was the first ESA approved by the FDA for use in renal failure (1989). Subsequently two ESAs were approved for the management of the anemia of cancer treatment (chemotherapy) of non-myeloid neoplastic disease: epoetin (1993) and darbepoetin alpha (2002).

B. FDA reviewed results of the Breast Cancer Erythropoietin Trial (BEST) and Henke studies. Concerns regarding an increased rate of tumor progression and increased mortality were incorporated into the Precautions Section of product labeling in 2004.

C. FDA convened a meeting of the Oncologic Drugs Advisory Committee 5/4/2004 to discuss safety issue for ESAs. The briefing information and transcript for the meeting is available at www.fda.gov/ohrms/dockets/ac/cder04.html#Oncologic.

D. In conjunction with the FDA, Amgen issued a "Dear Doctor Letter" regarding the use of ESAs for anemia management in the absence of chemotherapy, which was sent 1/26/2007.(See www.fda.gov/medwatch/safety/2007/safety07.htm#Aranesp)

E. Serial FDA ALERTS regarding ESA safety information were issued: 11/16/2006, 2/16/2007, and 3/09/2007.

F. FDA strengthened its warning about cardiovascular and thrombotic events in a variety of populations via a BLACK BOX warning. A "black box" warning is the most serious warning placed in the labeling of a prescription medication. FDA included BLACK BOX warnings for tumor progression and decreased survival in cancer patients undergoing cancer treatment. FDA also warned that ESAs are not indicated for anemic cancer patients not undergoing treatment and that mortality is increased when ESAs are used by this population. Specific warnings on the use of ESAs included that they:

- shortened the time to tumor progression in patients with advanced head and neck cancer receiving radiation therapy when administered to target a hemoglobin of greater than 12 g/dL,

- shortened overall survival and increased deaths attributed to disease progression at 4 months in patients with metastatic breast cancer receiving chemotherapy when administered to target a hemoglobin of greater than 12 g/dL,
- increased the risk of death when administered to target a hemoglobin of 12 g/dL in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. ESAs are not indicated for this population.

G. FDA convened a meeting of the Oncologic Drugs Advisory Committee (ODAC) on May 10, 2007 to discuss updated risk information on ESAs for the indication of cancer. The ODAC transcripts were recently posted at http://www.fda.gov/ohrms/dockets/ac/cder07.htm#OncologicDrugs.

VI. General Methodologic Principles

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. Critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that are used to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix B. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, the blinding of readers of the index test and reference test results.

Public comment sometimes cites the published clinical evidence and gives CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum.

VII. Evidence

1. Introduction

We are providing a summary of the evidence that we considered during our review. CMS extensively reviewed the body of literature on the use of ESAs in its proposed decision memorandum released on May 14, 2007. (http://www.cms.hhs.gov/mcd/viewdraftdecisionmemo.asp?id=203). We will not review that evidence again in this final decision. We refer the reader to Appendix A for a full discussion.

This section presents the agency's evaluation of the evidence considered for the assessment questions:

1. Is the evidence sufficient to conclude that erythropoiesis stimulating agent therapy affects health outcomes when used by Medicare beneficiaries with cancer and related neoplastic conditions?

2. If the answer to Question 1 is affirmative, what characteristics of the patient, the disease, or the treatment regimen reliably predict a favorable or unfavorable health outcome?

We will review each of the questions in the context of our proposed individual coverage criteria separately, respond to comments on that recommendation, discuss any new evidence, and provide our response with any proposed changes. Our responses to comments on aspects of the proposed decision other than the proposed coverage criteria are summarized in the Comment Section.

Multiple studies have raised significant safety concerns about the potential for ESAs to increase tumor progression and decrease survival in cancer patients. Although some of these were studies of ESAs used during radiotherapy or for anemia of cancerboth off-label usesthe data nonetheless raises concerns about the use of ESAs for all cancer indications to include labeled indications.

Because tumor progression has now been seen in some cancer patients, we believe that to demonstrate improved health outcomes, all ESA indications need evidence demonstrating that they do not cause tumor progression and/or decrease survival even if they might decrease transfusions or improve quality of life. In concert with our general methodologic principles (Appendix B), we believe that in most instances, this evidence can only be obtained in randomized controlled trials.

Several commenters questioned CMS' references in the proposed decision to basic science literature rather than solely to clinical trials. We emphasize that the safety signals came from randomized controlled clinical trials. Our review of other literature was to shed light on the possible underlying biological processes that may account for the trial findings. This was not a shift in CMS' stated preference for methodologically robust clinical evidence in determining whether health outcomes are affected by various technologies.

We remain concerned that a number of trials have been terminated, suspended, or otherwise not completedpossibly due to signals of harmand that the existing fund of published evidence may reflect a bias toward ESA use. Transparent public access to clinical trial datasets, as opposed to data summaries, would enhance public confidence in this body of literature.

2. External Technology Assessments

Please refer to the Proposed Decision Memorandum for a review of this matter. (http://www.cms.hhs.gov/mcd/viewdraftdecisionmemo.asp?id=203)

3. Internal Technology Assessment

Systematic reviews are based on a comprehensive search of published materials to answer a clearly defined and specific set of clinical questions. A well-defined strategy or protocol (established before the results of individual studies are known) is optimal.

CMS staff extensively searched Medline (1988 to present) for primary studies evaluating ESA therapy in cancer and related conditions. The emphasis was on studies structured to assess adverse events and mortality. CMS staff likewise searched the Cochrane collection, National Institute for Health and Clinical Excellence (UK) appraisals, and the Agency for Healthcare Research and Quality (AHRQ) library for systematic reviews and technology assessments. Systematic reviews were used to help locate some of the more obscure publications and abstracts. Preference was given to English publications.

Because much of the material remains outside the domain of the published medical literature, additional sources were used. CMS examined FDA reviews of the registration trials for epoetin and darbepoetin alpha as well as the FDA safety data for epoetin and darbepoetin alpha. CMS reviewed the transcripts and briefing documents (FDA and pharmaceutical sponsor) from the 2004 FDA Oncologic Drugs Advisory Committee (ODAC) meeting on ESA safety. CMS reviewed the FDA ESA drug safety alerts and label changes. CMS searched the National Institutes of Health (NIH) Clinical Trials.gov database for ongoing/completed trials of ESAs. CMS used internet searches to identify websites with clinical trial results, press releases for clinical trial termination, and U.S. government regulatory action. We catalogued these trials in our proposed decision (Appendix A).

Following the release of the proposed NCD on May 14, 2007, we received some additional references, primarily non-Medline publications. We also updated our search and broadened it to be more inclusive for MDS and multiple myeloma. We received over 300 additional citations as comments. Many of these addressed the blood supply, transfusion errors and erythropoietin receptors. We received many articles that duplicated items in our library. We also received numerous non-Medline abstracts. We did not receive any substantive raw data for analysis. The clinical trial tables have been updated to reflect the additional data.

Published Trials of ESA Use in Cancer

More than 100 papers or abstracts on ESA use in cancer have been published. Most studies have not been structured to assess survival, tumor progression and adverse events. Many studies enrolled patients with a variety of tumors. Others enrolled patients with a single disease, but were not stratified for tumor stage. Many studies included patients on a variety of treatment regimens. Many were not randomized, placebo-controlled trials. Many studies used another ESA as an active control. Most studies did not use fixed ESA doses, instead they titrated doses upward in poor responders without a statistical analysis that took this variability into account. Concomitant iron administration limited to patients in the ESA cohort was sometimes a confounding variable. Study endpoints were hemoglobin thresholds, changes in hemoglobin, transfusion requirements (without *a priori* definition), or quality of life. Frequently, the hematologic endpoint was a composite based on either a change in transfusion needs or hemoglobin level. Many studies did not declare a primary endpoint. Survival and/or tumor progression, if assessed, were secondary or add on endpoints. No studies presented *a priori* power calculations for patient number and study duration that would be required to demonstrate clinically significant survival differences for neoplastic diseases. No studies presented *a priori* methods for the assessment of tumor progression. Stratification of risk by tumor type, tumor stage, treatment modality, ESA dose, or ESA response to dose was not present in any of the studies reviewed. The additional data reviewed following the proposed decision did not change these conclusions (See Tables 2 and 3).

4. Medicare Evidence Development and Coverage Advisory Committee (MedCAC)

A MedCAC meeting was not convened for this issue.

5. Evidence Based Guidelines

There were no additional guidelines provided to CMS during the comment period. We describe guidelines in Appendix A.

6. Professional Society Position Published Statements

CMS received many comments from persons affiliated with various organizations. We distinguished bona fide position statements from professional organizations in part by determining if the author was identified as the president, executive vice president, executive director or equivalent of the society and if the comment was stated to be the position of the society rather than of an individual. All of these commenters disagreed with some provision of the proposed decision. In general, all thought that the decision was too restrictive. Some questioned CMS' legal authority to make this decision. We have summarized their input in Table 4 of the appendices; the full texts of their comments are available on our website (http://www.cms.hhs.gov/mcd/viewpubliccomments.asp?nca_id=203). All of their comments focused on one of the proposed criteria and we respond to those below where we separately review each of our proposed determinations.

7. Industry comments

We received comments from both marketers of ESAs in this country. They presented similar recommendations that supported the following noncovered indications in the proposed decision:

- Indication 1. Any anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding or bone marrow fibrosis
- Indication 3. Anemia of myeloid cancers (specifically AML/CML, not multiple myeloma)
- Indication 6. Anemia associated with radiotherapy (primary treatment)
- Indication 7. Prophylactic use to prevent chemotherapy-induced anemia (in patients who have never suffered from CIA)
- Indication 8. Prophylactic use to reduce tumor hypoxia
- Indication 9. Patients with erythropoietin-type resistance due to neutralizing antibodies
- Indication 12. Anemia due to cancer treatment if patients have uncontrolled hypertension

They did not agree with the other proposed noncovered indications:

- Indication 2. Anemia of myelodysplasia
- Indication 10. Patients with treatment regimens including anti-angiogenic drugs such as bevacizumab
- Indication 11. Patients with treatment regimens including monoclonal/polyclonal antibodies directed against the epidermal growth factor (EGF) receptor
- Indication 13. Patients with thrombotic episodes related to malignancy

Furthermore, they recommended several changes to the restrictions on the covered indications:

- The starting hemoglobin level should be 11 g/dL
- There should be no maximum dose
- For patients whose hemoglobin does not rise > 1 g/dL in the 4 weeks, two dose escalations should be allowed
- Patients with a rapid rise in hemoglobin should have a dose reduction
- ESA use should be discontinued when the hemoglobin level is 12 g/dL

We respond to these below where we separately review each of our proposed determinations.

8. Public Comments

Initial comment period: 3/14/2007 - 4/13/2007

We received 70 comments during the initial public comment period. Of the public commenters who furnished this information, 37 were from providers, 5 were from caregivers, 1 was from a patient, 13 were from professional organizations, 7 were from patient advocacy groups, 1 was from a national oncology policy consulting group and 2 were from pharmaceutical companies. Two comments regarding the use of ESAs for renal disease and two related to code assignments are included in the 70; both topics are outside the scope of this NCD.

The majority of commenters requested CMS to provide coverage of ESAs for all non-renal FDA approved indications. Several commenter included studies and scientific literature with their comments.

CMS received 2641 comments on the proposed decision. Several individual commenters submitted multiple comments; in some cases the same comment was submitted more than once by the same commenter. It appears in quite a few instances that many clinical and/or administrative support staff members from a single medical practice submitted comments. Some commenters submitted identical comments.

Most commenters did not refer to or provide any scientific or medical evidence that had not already been reviewed in the proposed decision memorandum or that could definitively answer the outstanding safety questions surrounding ESAs. However, we received a comment from Michael Henke, MD, Professor of Medicine/Radio Oncology at the University of Freiburg, Germany, the principal investigator from one of the trials that demonstrated the safety concerns. He states, "I am convinced that ESA treatment negatively affects disease control and survival of head and neck cancer patients." He further states that confirmed findings (RTOG 99 03 and DAHANCA 10) and his own research (Henke 2003) support this view. Dr. Henke indicated that comparable safety concerns can be assumed for other cancer sites as well, for example, Leyland Jones (2005) and Wright (2007) suggest breast and lung cancer.

Many commenters described their current clinical practice or current specialty guidelines. Of the physicians who commented, almost all were self-identified as hematologists and/or oncologists. CMS staff also received comments during meetings with representatives of Amgen, Ortho Biotech-Johnson & Johnson, Genentech, ASCO, US Oncology, Marti Nelson Cancer Foundation, Colorectal Cancer Coalition, and other institutions. Each organization used these meetings to emphasize their formal comments which are available online and summarized elsewhere in this document.

Almost all commenters disagreed with some provision of the proposed decision. Some commenters expressed agreement with some aspects of the proposed decision while disagreeing with other aspects. Some commenters did not express approval or disapproval. Thus, the count of commenters is a different number than the count of opinions of the commenters. Consequently, we will provide a summary of the different opinions and not the number of commenters supporting any specific opinions. Myelodysplasia was the subject of the largest number of comments about a specific clinical condition. Commenters also frequently speculated on the effect of the proposed decision on the need for transfusions and the adequacy of the blood supply to meet higher demands.

Subjects outside of the scope of this decision

Comment

Several commenters discussed the use of ESA therapy in the setting of anemia related to kidney disease or other uses that are beyond the scope of the proposed decision.

Response
We will not address those comments in this decision memorandum.

Personal or family member experience
Comment
Many commenters noted personal, friend, or family experience with ESA therapy. We heard from many cancer patients attesting to the benefit of ESAs regarding their quality of life. Beneficiaries submitted testimonies describing activities that were no longer difficult or impossible as a result of ESA therapy. Family members of beneficiaries receiving ESA therapy expressed concern over the costs of ESAs should CMS no long provider coverage. They expressed anger at Medicare for burdening them with the costs of ESAs. Beneficiaries and family members commented about their belief regarding the benefit and necessity of ESA therapy, adding that they would be forced to find a means to incur the costs.

Response
CMS carefully reviewed all the concerns submitted to us. We appreciate the comments received from the beneficiaries we serve and their families. We want our beneficiaries to have access to appropriate and quality care. While personal experiences are important and helpful to the Agency in understanding the impact of its decisions, CMS generally gives greater weight to published scientific evidence.

Lack of transparency/access regarding primary ESA data
Comment
Several commenters noted that it has been difficult if not impossible to obtain access to primary data from ESA clinical trials, and that this has made it problematic to have independent analyses of these data. They voiced support for measures that would increase public access to these data.

CMS received a comment from Marcia Angell, MD, Senior Lecturer in Social Medicine, Harvard Medical School, Former Editor in Chief, *New England Journal of Medicine (NEJM.)* who also expressed concern regarding the lack of transparency and access of primary ESA data. She states, "Medicare should have access to all the clinical trial information that the FDA has. Currently, companies seeking marketing approval must submit to the FDA all trials, not just the positive ones, but the agency generally does not share this information without the permission of the sponsoring company. That puts the proprietary interests of drug companies ahead of the public interest. Medicare should require full disclosure from the FDA as a condition of its support."

Response
We agree with the need for greater access to these unpublished datasets.

Blood supply and transfusion demand

Comment
Several commenters asked CMS to consider the effect of ESA use on the blood supply, i.e. blood available for transfusion, if the final decision resulted in more transfusions. Commenters expressed concern that shortages in the blood supply commonly exist and is a particular problem in some minority populations.

Response
The concern about the adequacy of the nation's blood supply is not a relevant factor for consideration in this national coverage determination. Our focus is whether the use of ESA is reasonable and necessary to treat a particular illness.

Financial considerations
Comment
Some commenters alleged that the specific provisions of the decision were prompted by CMS financial concerns. Some allege that we are trying to save money. Others suggest that the proposed decision would result in increased Medicare expenditures.

Response
The specific provisions of the proposed decision were derived from the regimens, including doses and durations of treatment, that were studied in clinical trials. We did not consider financial implications for these issues. Whether the decision ultimately affects Medicare expenditures is not a consideration in conducting national coverage analyses.

Quality of life as a research outcome
Comment
Many professional societies suggested that quality of life (QoL) outcomes should be a sufficient research endpoint. They urged CMS to use QoL outcomes as evidence to make a reasonable and necessary determination for coverage. For example, the American Society of Hematology (ASH) submitted a list of supporting evidence that included literature pertaining to QoL as an outcome measure for patients with cancer receiving ESA therapy.

Response
Wisloff et al. examined the impact of hemoglobin concentration on QoL scores in 745 patients with multiple myeloma. They had the following conclusion:

"When examining the effect of haemoglobin on QoL, it is essential to adjust for disease parameters and response to therapy in order not to overestimate the impact of haemoglobin on QoL. Our findings imply that uncontrolled studies on the effect of erythropoietin (EPO) in cancer patients may be making exaggerated claims for the effect of EPO on QoL" (Wisloff 2005).

We believe that there is currently insufficient evidence to postulate a QoL benefit to support ESA use. Such evidence of benefit, if one indeed exists, requires more robust research than we have reviewed to date. However, even if such evidence existed, it would need to be weighed against the new evidence suggesting tumor progression and increased mortality.

Pediatric populations
Comment
Some commenters suggested that the proposed decision would adversely effect pediatric populations.

Response
Infants and young children with cancer or leukemia are generally not Medicare beneficiaries. Any issues peculiar to the pediatric population are not generalizable to the Medicare population at large.

Coding
Comment
We were asked to provide ICD-9 codes with the policy.

Response
We do not provide coding instructions in NCDs. We do, however, consider coding in the instructions that are developed to direct our contractors who process claims for items and services billed to Medicare.

CMS authority to make the NCD
Comment
A commenter contested CMS' authority to limit reimbursement for ESA therapy, claiming that toxicity is not relevant to decisions about medical reasonableness. Other commenters suggest that, under Section 1861(t)(2) of the Social Security Act, Medicare cannot establish coverage conditions for ESA use in the context of anticancer treatment.

Response

We disagree with these comments. CMS' authority to develop and implement NCDs is clearly and unequivocally established in statute. In determining if a particular drug is reasonable and necessary, one of several considerations is whether the drug improves health outcomes. In this context, toxicity is relevant in determining if health outcomes are improved.

Section 1861(t)(1) of the Social Security Act defines the terms "drugs" and "biologicals." The statute at § 1861(t)(2) defines a subset of "drugs," those used in an anticancer chemotherapeutic regime for a medically accepted indication. ESAs may fall under either definition, depending on the use.

The definitions of drugs and biologics at § 1861(t)(1) & (t)(2) include listings in compendia. The United States Pharmacopoeia-Drug Information (USP-DI) is a compendium that lists accepted and unaccepted uses of drugs. Both epoetin and darbepoetin alpha are included in USP-DI and have listings that were changed after the FDA released its black box warning.

Prior to the changes made in March of 2007 in the USP-DI, both darbepoetin alpha and epoetin had accepted indications for the treatment of anemia in cancer patients when the anemia was due to chemotherapy. Epoetin had an off-label indication for treatment of chronic anemia associated with neoplastic diseases. Darbepoetin alpha had an unaccepted indication for treatment of anemia of cancer not due to chemotherapy.

Following the FDA black box warning, the darbepoetin alpha unaccepted indication was strengthened with additional data. The epoetin section also had additional language added that stated that epoetin improves anemia due to cancer in patients not receiving chemotherapy, but may compromise survival. Additional language in the cancer treatment section stated that epoetin has not demonstrated improvements in cancer outcomes and may compromise survival. In sum, the current US-PDI compendium listings provide unfavorable evaluations for these drugs.

Finally, we emphasize that Medicare NCDs instruct our contractors on the coverage of items or services for which claims are made. NCDs do not direct physicians regarding the provision of any particular item or service.

ESA overuse and revision of treatment guidelines

Comment

A commenter said in part that ESAs are overused and suggested that revised guidelines and a lower upper threshold could allow continued use of these agents in those patients who would benefit.

Response
We agree.

Preserving appropriate access
Comment
Y-ME National Breast Cancer Organization stated that breast cancer patients should have access to medications, including ESAs if appropriate, and noted that a significant portion of breast cancer patients are Medicare beneficiaries.

Response
We did not propose to eliminate coverage to ESA therapy for beneficiaries with breast cancer, though we did propose limitations on the dosing that would be covered by Medicare. We believe that our final decision preserves appropriate access with due attention to the serious concerns that are reflected in the FDA black box warnings, the discussions of the ODAC, and the evidence we reviewed.

ESAs are equivalent
Comment
Several commenters stated that ESAs have the same effects and should be treated similarly in this decision.

Response
We agree.

Need for more clinical trials
Comment
Several commenters pointed out that more clinical trials are needed to answer important outstanding questions.

Response
We agree.

ESAs as anti-tumor therapy

Comment

Commenters stated that current data do not support ESA use solely to potentiate the effectiveness of anti-tumor therapy.

Response

We agree.

CMS and FDA

Comment

A commenter said that FDA approved labeling indicates when treatment is "necessary." Other commenters made various comments about FDA processes.

Response

The labeled indication for the treatment of anemia related to chemotherapy is to decrease the need for transfusions in patients who will be receiving concomitant chemotherapy. The FDA approved label does not identify a hemoglobin (or hematocrit) level at which ESA therapy may be indicated or necessary to treat anemia in patients who have cancer that is related to receiving chemotherapy. However, the FDA label does identify hemoglobin (or hematocrit) levels at which ESA therapy may be indicated, or necessary for the treatment anemia related to chronic renal failure, and for anemic patients scheduled to undergo elective, non-cardiac, nonvascular surgery. Some commenters were confused and believed that the FDA label did, in fact, identify a specific hemoglobin/hematocrit level at which ESA therapy may be indicated or necessary to treat anemia related to chemotherapy.

CMS is not changing the FDA indication for ESA therapy for cancer patients who have anemia related to chemotherapy. CMS' coverage provision is the FDA label indication and ensures that cancer beneficiaries who have anemia related to chemotherapy can avoid transfusions by receiving ESA therapy "that will gradually increase the hemoglobin (or hematocrit)concentration to the lowest level sufficient to avoid the need for transfusion", as stated in the FDA labeled Black Box Warning.

CMS and FDA are separate agencies with different statutory missions, and operate under distinct legal authorities. CMS cannot address these comments about FDA's processes. They should be addressed to FDA directly.

FDA and ODAC

Comment

Several commenters requested that CMS delay rendering a proposed decision until after the FDA ODAC meeting scheduled for May 11, 2007. Other commenters suggested that we defer any final decision until the FDA has responded to the ODAC recommendations. Commenters suggested that CMS review the literature and data distributed at the ODAC meeting prior to rendering the proposed decision. Others asked if we have consulted with FDA or suggested that we consult with FDA.

Response
As stated above, CMS and FDA are separate agencies with different statutory missions, and operate under distinct legal authorities. CMS independently reviewed the evidence prior to the ODAC meeting, which was attended by CMS staff. The concerns raised and the evidence discussed at the ODAC are consistent with the body of evidence that we had already reviewed. We are encouraged that the separate and independent analyses of the FDA and CMS have raised similar serious concerns about the use of ESA treatment in patients with cancer and related neoplastic conditions. CMS' proposed decision was published after the ODAC meeting. FDA deliberations are not public and their timeline for making changes (if any are made) in the labeling for ESAs is unknown. We believe the safety concerns that we have identified in this document required CMS to act quickly to protect beneficiaries.

Acceptable risk
Comment
A number of commenters acknowledged risks associated with ESA use but said that among individual patients there will be different judgments made by patients about what risk is acceptable in light of their personal values, religious beliefs, disease severity, and other factors. They propose that patients and physicians should be allowed to make those decisions without CMS influence.

Response
We agree that treatment decisions regarding the use of ESAs shall be made by physicians and patients, making sound judgments about the risks associated with ESA therapy. In making national coverage determinations, we review the applicable evidence and may, as appropriate, make determinations wherein Medicare coverage for certain items and services is not reasonable and necessary. Thus, in this instance, CMS is making a determination as to those circumstances under which ESA use in patients with cancer and related neoplastic conditions is or is not reasonable and necessary.

9. Expert Opinion

CMS received numerous responses from individuals and organizations that could be classified as “expert.” Due to the large number of these comments, we will not separately include those here. We will limit discussion under this heading to a summary of the FDA Oncologic Drugs Advisory committee (ODAC).

FDA convened the ODAC on 5/10/07 to consider ESA use in cancer. Background materials are available at: fda.gov/OHRMS/DOCKETS/ac/07/briefing/2007-4301b2-02-FDA.pdf (*accessed 05/25/07)*. The ODAC transcripts are available at fda.gov/ohrms/dockets/ac/cder07.htm#OncologicDrugs (accessed 07/03/07).

Included among the recommendations made by the ODAC to FDA are:

- further marketing authorization be contingent upon additional restriction in product labeling;
- further marketing authorization be contingent upon additional trials;
- labeling should specifically state that ESAs are not indicated for use in specific tumor types that may include breast cancer, head and neck cancer, and non small-cell lung cancer (NSCLC);
- the current evidence is insufficient to determine a lower limit different from the current level of 10 g/dl;
- the current evidence is insufficient to determine an upper limit different from the current level of 12 g/dl; and
- product labeling should recommend discontinuation of the ESA following completion of a chemotherapy regimen and re-evaluation of the degree of anemia with subsequent chemotherapy regimen.

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act, § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member" (§ 1862(a)(1)(A)). This section presents the agency's evaluation of the evidence considered and conclusions reached for the assessment questions:

1. Is the evidence sufficient to conclude that erythropoiesis stimulating agent therapy affects health outcomes when used by Medicare beneficiaries with cancer and related neoplastic conditions?

2. If the answer to Question 1 is affirmative, what characteristics of the patient, the disease, or the treatment regimen reliably predicts a favorable or unfavorable health outcome?

As discussed above, CMS considers improved health outcomes in its reasonable and necessary determinations. Because multiple studies have demonstrated increased tumor progression and decreased survival in certain cancer patients, there may be the potential that the ESA stimulated tumor progression and increased mortality seen in these few cancers may be seen in other cancers. Thus, we believe that in order to demonstrate improved health outcomes, we need to review evidence that demonstrates that ESAs do not cause tumor progression and/or decrease survival in these other cancers even if they might decrease transfusions or improve quality of life.

Thus, in order to assess the evidence for questions 1 and 2, we consider whether the evidence is robust and demonstrates that the use of ESAs in any cancer patient decreases transfusion requirements and/or improves survival and, if so, does the evidence demonstrate that the use of ESAs does not increase tumor progression or decrease survival?

For the convenience of the reader we have organized our analysis by the coverage criteria in our proposed decision. Following a general discussion, we will in each case:

- review public comments;
- discuss any additional evidence presented during the comment period;
- annotate the FDA labeling for that criteria;
- annotate the recommendation in the United States Pharmacopoeia-Drug Information (USP-DI), a compendium that lists accepted and unaccepted uses of drugs;
- evaluate the assessment questions above (see Section VII.1);
- respond to the comments and evidence; and
- summarize our decision.

General Discussion

In a typical setting, physiologic replacement of a missing hormone should result in normalization caused by that deficit. Indeed many, albeit not all, patients with ESRD are deficient in erythropoietin because of damage to the renal parenchyma. Their anemia is secondary to and highly responsive to low doses of ESAs. In other settings, a hormone is used at higher than physiologic levels because of hormone resistance or to supplement endogenous pathways to achieve superphysiologic or accelerated physiologic responses.

Early ESA drug development was based on the typical setting of a deficit in erythropoietin action. The endpoints in the clinical trials were reduction in the transfusion rate, quality of life, absolute hemoglobin level, and change in hemoglobin level. The hemoglobin parameters were surrogate endpoints. Because anemia portended poor clinical outcome (Dunphy 1989; Fein 1995; Obralic 1990; Oehler 1990; Reed 1994), it was hypothesized that reversal of anemia itself would improve long-term clinical status. It was presumed that the primary risk was thromboembolic vascular events, and that these were related to hemoglobin level rather than to drug dose and/or response to drug dose. As such, most of the registration trials for FDA approval were relatively small and conducted in heterogeneous patient populations with a mixture of primarily solid tumors at various stages who were undergoing treatment with a variety of regimens. (See Proposed Decision Memorandum-drug registration section (http://www.cms.hhs.gov/mcd/viewdraftdecisionmemo.asp?id=203))

At the time of initial drug approvals for cancer-treatment associated anemia, the FDA had concerns about ESA mediated tumor initiation or promotion. The FDA requested post-approval Phase IV commitments in 1993 and 2002 to explore this putative risk promotion because the registration studies were not structured to assess overall survival, cause-specific mortality, cause-specific morbidity, tumor-free survival, and tumor progression. The post approval studies permitted heterogeneous patient populations because it was presumed that the risk benefit ratio would be similar for all tumors at all stages, for all treatment modalities, and in all adult patient populations. For a listing of Phase IV commitments, see Proposed Decision Memorandum sections on terminated trials and ongoing studies (http://www.cms.hhs.gov/mcd/viewdraftdecisionmemo.asp?id=203).

In many of the terminated trials, there was a signal suggesting decreased survival. Attribution for the precise determination of mortality cause was often not done or not done rigorously. Nonetheless, results from studies that attempted to assess cancer disease-free survival or changes in locoregional tumor control, suggest that tumor progression plays a more significant role than vascular-thrombotic events in the apparent decreased survival observed with ESA use for the anemia secondary to cancer chemotherapy, an FDA approved indication. A signal for decreased survival was also observed with ESA use for the anemia of cancer (in patients not undergoing chemotherapy) and to reduce tissue hypoxia during radiation treatments, neither of which are FDA approved indications. These observations have resulted in FDA Black Box warnings, the most serious warning placed in the labeling of a prescription medication (see section III (V) F).

Tumor progression might occur via a number of avenues. Malignant cells could be transformed, or their milieu enriched. The first mechanistic pathway includes the ability of malignant cells to survive via decreased programmed cell death (apoptosis), the ability to survive through resistance to chemo/immuno/radiotherapy, increased proliferation leading to greater tumor burden, enhanced invasiveness, and improved migratory or metastatic travel capacity. Another mechanistic pathway includes decreased tissue hypoxia and increased nutrient supply via a more extensive vascular network (angiogenesis) and increased erythrocyte number.

In the absence of definitive clinical data we have reviewed significant amount of in vitro work to support the first pathway (Acs 2001, 2002, 2003; Anagnostou 1990, 1994; Arcasoy 2003, 2005; Batra 2003; D'Andrea 1989; Digicaylioglu 1995; Farrell 2004; Fraser 1989; Haroon 2003; Henke 2006, Jones 1990; Kumar 2006; Lai 2005; Lappin 2003; Masuda 1993; Mioni 1992; Ogilvie 2000; Ribatti 2003; Rossert 2005; Selzer 2000; Westenfelder 2000; Wright 2004; Winkelman 1990; Yasuda 1998, 2001, 2006). Indeed, elements of the erythrocyte receptor signaling cascade are similar to those of epidermal growth factor (EGF) receptor, a target against which immunotherapeutic agents are being developed (Wakao 1997; Zhang 2006). Locoregional progression of head-and-neck cancer was increased in patients with tumors positive for erythropoietin receptors and who were treated with erythropoietin (Henke 2006). There is a trend for such progression even in the patients with erythropoietin receptors who did not receive erythropoietin, suggesting that endogenous erythropoietin might be variable and able to impact clinical outcome (Henke 2006). Cultured cells (cervical cancer line HT100 and glioma line U87) developed resistance to ionizing radiation and cis-platinum after exposure to erythropoietin (Belenkov 2004; Yasuda 2003). Incubation with an inhibitor to the erythropoietin receptor's JAK-STAT pathway, typhostin (AG490), could reverse this resistance (Belenkov 2004).

The picture, however, is not straightforward. As such, universal statements about how ESA use results in the outcomes seen in oncology cannot be made. Erythropoietin receptor number may change with the cell cycle (Acs 2001; Broudy 1991). The number may increase with the stage of the tumor (Acs 2001). Some cell lines do not exhibit proliferation in response to erythropoietin exposure (Wesphal 2002). Indeed, Henke et al. found that locoregional progression of head-and-neck cancer was not increased in erythropoietin-treated patients lacking erythropoietin receptors (Henke 2006). Mittelmann et al. even found myeloma regression in mice after ESA treatment (Mittelmann 2001). Tovari et al. found that ESA treatment might enhance sensitivity to 5-fluorouracil chemotherapy (Tovari 2005).

There is also a significant amount of *in vitro* work that supports the second mechanistic pathway. Microvascular density and tumor stage (for neuroblastomas and hepatocellular carcinomas) have been found to correlate with both erythropoietin and erythropoietin receptor expression (Ribatti 2007 A&B). This suggests that there is tumor secretion of erythropoietin that binds to erythropoietin receptors on vasculature which, in turn, proliferates and further promotes tumor growth (Ribatti 2007 A&B). Secretion of pro-angiogenic factors and recruitment of vascular endothelium has also been observed with human mesenchymal stem cells which, like cancer cells, are less differentiated than normal cells (Zwezdaryk 2007). There has even been a report of the conversion of myelodysplastic syndrome (MDS) to leukemia attributed to erythropoietin's angiogenic effects on the bone marrow (Bunworasate 2001; Ribatti 2002). Indeed anti-angiogenic monoclonal antibody therapy has been approved for colon cancer and is under development for other tumors (Panares 2007). Nonetheless, erythropoietin-induced angiogenesis has not been found in all cancers or test models (Hardee 2005).

Oncology patients may be exposed to supraphysiologic ESA doses. Many cancer patients manifest erythropoietin resistance, i.e., they have an inappropriately low endogenous erythropoietin response to anemia (Ward 1977) and do not respond to low exogenous dose levels (Miller 1990). This is likely to be compounded in geriatric patients who are known to have reduced hematopoietic reserve (Miller 1990). Less frequent dosing regimens, although equivalent to more frequent dosing regimens on the basis of a hematologic response, result in higher peak blood levels of hormone (Chung 1998, 2001; Kryzunski 2005; Ramakrishnan 2004). It is not known whether supraphysiologic ESA blood levels would increase the likelihood of spill-over from the classic high affinity erythropoietin receptor binding sites in the bone marrow to non-marrow receptors with different binding constants where it can act as a growth factor (Fraser 1988, 1989; Masuda 1993; Hardee 2006) or whether excess hormone is bound by the soluble erythropoietin receptors secreted by some tumors (Harris 1996; Maeda 2001; Wesphal 2002).

Regardless of the cause(s), careful prospective trials controlled for the tumor, tumor stage and perhaps tumor cell cycle, cancer treatment, and perhaps endogenous systemic or paracrine/autocrine erythropoietin production and the presence of erythropoietin receptor on tumors and as soluble elements in the blood are needed to inform practitioners as to whether ESAs provide a meaningful clinical benefit for the various oncologic populations. Careful trials would also assess the effects of dose including doses in patients who exhibit a poor hematologic response to low doses as well as the effects of long-term dosing and repeated dosing.

We cannot be sure of the completeness of the evidentiary database because of the question of unpublished data. Negative studies were frequently not available as full published reports on Medline. The early termination of studies by data safety monitoring boards, investigators, and/or pharmaceutical sponsors because of a safety concern does not permit complete appraisal of the magnitude of safety risk. Early termination may reduce the statistical power of a safety finding. Nonetheless, evidence of harm is apparent despite these limitations. ESA treatment has been associated with an increased risk of thrombotic-vascular disease, tumor progression, and decreased survival. Furthermore, there are potential mechanisms that could explain the etiology of the harm.

Although the evidence is less robust than we would like, particularly for geriatric patients, it is sufficient to identify certain patient characteristics and treatment practices that have a high likelihood of unfavorable clinical outcomes. In our proposed decision, we identified several instances in which this high likelihood occurred. Additionally, we proposed that for other indications, we limit use of ESAs to tumors with erythropoietin receptors and to specific targets that we felt the evidence supported. Use of ESAs in other tumors was left to contractor discretion.

The following subsections will discuss each indication separately and any changes to what we proposed.

Analysis by Specific Indications

Proposed Noncovered Indication #1: Any anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis

Public Comments
Commenters on this issue supported the CMS proposed decision. A majority of commenters agreed that use of ESAs for these indications was not supported by evidence. Two societies suggested that this indication be covered in the case of marrow fibrosis, but agreed with the rest of the restrictions.

Additional Evidence
We received no new evidence supporting the use of ESAs in the treatment of anemia in cancer patients due to the conditions listed.

We note that the current FDA labels for Epogen (epoetin) and Aranesp (darbepoetin alpha) respectively include the following relevant language.

EPOGEN (epoetin) is not indicated for the treatment of anemia in cancer patients due to other factors such as iron or folate deficiencies, hemolysis, or gastrointestinal bleeding, which should be managed appropriately.

A lack of response or failure to maintain a hemoglobin response with Aranesp (darbepoetin alpha) doses within the recommended dosing range should prompt a search for causative factors. Deficiencies of folic acid, iron or vitamin B12 should be excluded or corrected. Depending on the clinical setting, intercurrent infections, inflammatory or malignant processes, osteofibrosis cystica, occult blood loss, hemolysis, severe aluminum toxicity and bone marrow fibrosis may compromise an erythropoietic response.

We note that the USP-DI has similar language for both epoetin and darbepoetin alpha.

Response
We agree with the majority of the commenters who supported this decision. We were not presented evidence, nor did we find any evidence that would support the use of ESAs in marrow fibrosis. We are finalizing our decision of noncoverage for this indication.

Summary
We have determined that ESAs are not reasonable and necessary for any anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis.

Proposed Noncovered Indication #2: Anemia of myelodysplasia (MDS)

Public Comments
Commenters on this issue strongly opposed the CMS proposed decision. Many commenters referred to current clinical practice and longitudinal experience to support the use of ESAs in MDS. Others suggested that these data could be sufficiently inferred from existing published trials. Others expressed concern that continuing this noncoverage would markedly increase the transfusion rate and exhaust the available blood supply

Additional Evidence
Data was presented demonstrating that MDS patients on ESAs had fewer transfusions than had been historically needed for MDS patients prior to ESAs.

FDA: This is an off-label use.

USP-DI describes MDS as an "Acceptance not established" indication. MDS is not explicitly addressed in the USP-DI listing for darbepoetin alpha.

Response
We continue to believe that there is insufficient robust clinical evidence to support the coverage of ESAs for treatment of MDS. When we opened this NCD, we committed to looking at all non-ESRD uses of ESAs. However, in the proposed decision, we narrowed the scope of the NCD to cancer and related neoplastic conditions. MDS is not an oncologic disease; it is a premalignant condition. We note what is still lacking in this clinical field, are randomized clinical trials of appropriate duration, examining safety as a primary endpoint and powered sufficiently to determine whether use of ESAs in this population is ultimately beneficial or harmful; and if so, whether for all patients with MDS or only to specified subpopulations. While data does suggest that ESAs lower the number of transfusions in MDS patients, it is unclear if some or much of this decrease is from the general decrease in transfusions that occurred in a similar time frame to the introduction of ESAs.

Summary
MDS is not an oncologic disease; it is a premalignant condition. Thus, we believe it appropriate to not include this indication in this decision.

Proposed Noncovered Indications #3: Anemia of myeloid cancers

This indication is a subset of #5: Anemia of cancer not related to cancer treatment. We are collapsing this indication into that one.

Proposed Noncovered Indications #4: Anemia associated with the treatment of myeloid cancers or erythroid cancers

Public Comments
Commenters were most concerned about how CMS defined myeloid cancer. They requested that multiple myeloma be specifically excluded from this definition. They supported the CMS proposed decision to noncover use in acute and chronic myelogenous leukemias (AML and CML) and erythroid cancers.

Additional Evidence
We received no new published evidence that supports the use of ESAs during the treatment of CML, AML, or erythroid cancers.

The FDA approved label for Epogen (epoetin) includes the following language.

EPOGEN (epoetin) is indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy.

Aranesp (darbepoetin alpha) is indicated for the treatment of anemia associated with chronic renal failure, including patients on dialysis and patients not on dialysis and for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy.

The USP-DI has similar language for both epoetin and darbepoetin alpha.

Response
We agree that multiple myeloma is not included in the definition of myeloid cancer. We also agree with the commenters that the noncoverage for myeloid cancers be specifically linked to CML and AML. We clearly listed it among the solid tumors for which we proposed restricted coverage.

Summary
We will modify our proposed decision and define the specific myeloid cancers that are noncovered. We have determined that ESAs are not reasonable and necessary for any anemia associated with the treatment of CML, AML, or erythroid cancers.

Proposed Noncovered Indication #5: Anemia of cancer not related to cancer treatment

Public Comments
Most commenters were in support of this noncoverage, stating that this was the setting in which much of the adverse outcomes were reported. Some commenters suggested that in spite of the evidence, physicians should make individual decisions about the use of ESAs in this setting. Some beneficiaries with cancer stated that they received ESA therapy continuously for years. Others stated that they continue to receive ESA therapy, though their cancer is in remission. Some commenters suggested Coverage with Evidence Development (CED) for this indication.

Additional Evidence
We received no additional published evidence supporting the use of ESAs for the treatment of anemia not related to cancer. We were provided with observational data on the improvement in QoL scores in some patients who received ESAs while not under treatment. No data supported any improvement in other measures of morbidity or survival.

FDA: This is an off-label use. We note that the labels for Epogen/Procrit (epoetin) and Aranesp (darbepoetin alpha) include the following language in their black box warnings.

- increased the risk of death when administered to target a hemoglobin of 12 g/dL in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. ESAs are not indicated for this population.

In the USP-DI, epoetin is listed under the section 'Acceptance not established' with the language:

Epoetin improves anemia due to cancer in patients not receiving chemotherapy, but may compromise survival.

USP-DI lists darbepoetin alpha as not indicated ("unaccepted") for the treatment of anemia associated with neoplastic diseases.

Response
Use of ESAs in cancer not associated with treatment is the specific indication in which much of the reports of adverse events have occurred. While we agree that physicians and patients have the freedom to make independent treatment choices, this Agency must evaluate the relevant evidence and make determinations to ensure that Medicare coverage is provided only for items and services that are reasonable and necessary. In this case, we have determined that the use of ESAs for this indication is not reasonable and necessary. Moreover, this determination is supported by the strong FDA black box warning.

CMS uses coverage with evidence development when we believe there is some evidence of benefit but not to the point of national coverage. In this case, there is evidence of harm and thus we do not believe that CED is appropriate for ESA use for this indication.

Summary
The evidence we reviewed and the public comments support the determination that ESAs are not reasonable and necessary for any anemia in cancer that is not related to cancer treatment.

Proposed Noncovered Indication #6: Anemia associated with radiotherapy

Public Comments

The majority of commenters on this issue supported the CMS proposed decision. Those few that disagreed noted that in some cases (especially colorectal cancer) chemotherapy is given in concert with radiotherapy. They did not disagree with radiotherapy alone as being a limitation to coverage.

Additional Evidence
We received no additional evidence supporting the use of ESAs in the treatment of anemia associated with radiotherapy.

FDA: This is an off label use. We note that the labels for Epogen/Procrit (epoetin) and Aranesp (darbepoetin alpha) include the following language in their black box warnings.

- shortened the time to tumor progression in patients with advanced head and neck cancer receiving radiation therapy when administered to target a hemoglobin of greater than 12 g/dL.

The USP-DI has strong warnings for the use of ESAs for this indication.

The following language is included in the 'Unaccepted' section of the indications.

A non-significant trend towards reduced 1-year overall survival was reported in an additional abstract in patients with squamous cell carcinoma of the head and neck who received definitive radiotherapy with epoetin alfa (70%) versus those who did not receive epoetin alfa. In addition, the class of erythropoiesis-stimulating agents (ESA) has been noted in other clinical trials to have an increase in serious/life-threatening side effects and/or a detrimental effect on survival

We note the following language in 'Side/Adverse Effects'

The use of darbepoetin alpha in cancer patients when administered to target of greater than 12g/dL

- shortened the time to tumor progression in patients with advanced head and neck cancer receiving radiation therapy

Response
There is agreement on this issue by all commenters and CMS. To clarify, we are referring only to radiotherapy and not to concomitant chemotherapy.

Summary
The evidence reviewed and the comments received support the determination that ESAs are not reasonable and necessary for the treatment of anemia associated only with radiotherapy.

Proposed Indication #7: Prophylactic use to prevent chemotherapy-induced anemia

Public Comments
The majority of commenters on this issue supported the CMS proposed decision. A few commenters did advocate for prophylactic use in patients who were about to receive chemotherapy.

Additional Evidence
We received no additional evidence supporting the use of ESAs to prevent chemotherapy-induced anemia.

FDA: This is an off-label use.

USP-DI: This indication is not listed nor discussed in the USP-DI for epoetin or darbepoetin alpha.

Response
Given the evidence surrounding this and the public comments on this issue, this indication will remain non-covered.

Summary
The evidence reviewed and the comments received support the determination that ESAs are not reasonable and necessary for prophylactic use to prevent anemia in beneficiaries who have cancer.

Proposed Noncovered Indication #8: Prophylactic use to reduce tumor hypoxia

Public Comments
All commenters on this issue supported the CMS proposed decision.

Additional Evidence
We received no additional evidence supporting the use of ESAs to reduce tumor hypoxia.

FDA: This is an off-label use.

The USP-DI does not address this indication.

Response
We agree with the public comments received regarding this proposed decision.

Summary
The evidence reviewed and the comments received support the determination that ESAs are not reasonable and necessary for prophylactic use to reduce tumor hypoxia.

Proposed Noncovered Indication #9: Patients with erythropoietin-type resistance due to neutralizing antibodies

Public Comments
Most commenters on this issue supported the CMS proposed decision. One dissenting argument was that this provision was unrealistic since the assay is not clinically available and serves as a research tool.

Additional Evidence
We received no additional evidence supporting the use of ESAs in patients with erythropoietin-type resistance due to neutralizing antibodies.

FDA: We note the following language in the labels for Epogen (epoetin) and Aranesp (darbepoetin alpha).

EPOGEN (epoetin) should be permanently discontinued in patients with antibody-mediated anemia. Patients should not be switched to other erythropoietic proteins as antibodies may cross-react (see ADVERSE REACTIONS: Immunogenicity).

If anti-erythropoietin antibody-associated anemia is suspected, withhold Aranesp (darbepoetin alpha) and other erythropoietic proteins...Aranesp (darbepoetin alpha) should be permanently discontinued in patients with antibody-mediated anemia. Patients should not be switched to other erythropoietic proteins as antibodies may cross-react (see ADVERSE REACTIONS: Immunogenicity).

The USP-DI does not address erythropoietin resistance due to neutralizing antibodies.

Response
We recognize that this is not a commonly performed test. However, there is broad evidence to indicate that the use of ESAs in patients who, for any reason, have had this test performed with a positive result, may lead to negative outcomes. Given the favorable comments and the fact that we received no new evidence, this indication will remain noncovered.

Summary
The evidence reviewed and the comments received support the continuing determination that ESAs are not reasonable and necessary in beneficiaries with erythropoietin-type resistance due to neutralizing antibodies.

Proposed Noncovered Indication #10: Patients with treatment regimens including anti-angiogenic drugs such as bevacizumab

Public Comments
Commenters on this issue generally opposed the CMS proposed decision restricting the use of ESAs in patients receiving anti-angiogenic drugs. Commenters also contested our assumptions about the angiogenic effects of ESAs. Several commenters have noted that concomitant use with anti-angiogenic therapy is contraindicated. Several commenters noted that many chemotherapy drugs have some anti-angiogenic properties. Also, commenters suggested that the concern about the interaction of ESAs with anti-angiogenic drugs are only theoretical and have not been demonstrated in practice. Many supported CED in lieu of noncoverage when anti-angiogenic drugs are used alone. A manufacturer of an anti-angiogenic drug expressed concern that a specific drug was cited as an example, rather than referring to the class of drugs alone.

Additional Evidence
Published data evaluating the addition of ESAs to chemotherapy regimens including anti-angiogenic drugs were not available. One company presented an analysis of data from trials involving bevacizumab. In that analysis it separately evaluated outcomes on patients receiving ESAs and those not receiving ESAs and found no differences in outcomes.

FDA: This is a labeled indication.

The USP-DI does not list nor include any indication/discussion regarding treatment regimens including anti-angiogenic drugs for either epoetin or darbepoetin alpha.

Response

Angiogenesis appears to be important for both tumor growth and metastasis formation. Until neoplasms acquire the potential to induce vessel formation that can ensure adequate nutrition and oxygen, their growth is effectively held in check. Targeting angiogenesis is more focused than generalized cytotoxic or cytostatic therapy which targets all rapidly growing cells (Seimann 2005). Anti-angiogenesis can be achieved in several ways. Repeated small doses of chemotherapy can be given to semi-selectively poison the vascular epithelium (metronomic therapy). Other drugs do this by targeting growth factors (e.g. basic fibroblast growth factor [bFGF], platelet derive growth factor [PDGF], transforming growth factor [TGF], and vascular endothelial growth factor [VEGF]), their receptors, matrix metalloproteinases, and tumor suppressor gene activity (Bouis 2006; Svensson 2003; Zhong 2006).

Hardee et al. have provided some of the most compelling data for angiogenesis. Breast cancer cells injected into a window chamber imbedded in living mice showed evidence of vessel formation (angiogenesis) and tumor size progression that was greater than controls when the cells were exposed to erythropoietin (Hardee 2007). These changes occurred in the absence of differences in hematocrit levels. These findings could be blunted by any one of three inhibitors: recombinant soluble erythropoietin receptor, neutralizing monoclonal erythropoietin antibody, or mutant erythropoietin (competitive inhibition). There were similar findings of vessel proliferation and tumor progression, when breast cancer cells were genetically altered to include a mutant and constitutively active (always on) erythropoietin receptor. The findings from the window chamber assay were replicated in an assay using the mouse mammary fat pad.

Folkman has stated that the benefits of anti-angiogenic therapy might be limited by the redundancy or multiplicity of pathways for angiogenesis (Folkman 2006). Vascular endothelial growth factor (VEGF) is not the sole regulator of angiogenesis. Farrell and Lee state "…Ribatti and colleagues recently provided evidence that erythropoietin can also elicit an angiogenic response in endothelial cells in vitro and in vivo, and, thus, like VEGF, is an effective angiogenic factor…In agreement with the previous studies in human umbilical vein endothelial cells and bovine adrenal capillary endothelial cells, recombinant human erythropoietin substantially increased EA.hy926 cell proliferation. Furthermore, recombinant human erythropoietin exposure resulted in a three-fold greater matrix metalloproteinase 2 activity in treated EA.hy926 cultures compared with cell cultures grown in untreated media" (Farrell 2004). The first author of this paper is a Johnson & Johnson scientist.

It is not known whether the anti-angiogenic activity (efficacy) of these drugs are significantly diminished by the angiogenic activity of ESAs since prospective drug interaction studies have not been done. For the same reason, it is also not known whether 1) the cardiovascular complications, fluid retention, thrombosis, and hypertension observed with the anti-angiogenic monoclonal antibody, bevacizumab, are unique to the drug or are class effect and 2) the likelihood of these adverse effects, which also occur with ESAs, would be increased by combination use (Dear Doctor Letter with FDA warning 2004, 2006; USA Today 8/13/04). As we are modifying our proposed decision, CED is not an option.

Summary

Some evidence supports the pathophysiologic construct that ESAs can stimulate certain growth factors (VEGF, EGFR) that are the targets of chemotherapy. The appropriate evidence would be randomized trials that evaluate the addition of ESAs to standard treatment regimens. That evidence is not available. We have strongly considered, as many commenters suggested, whether this indication would be appropriate for CED. However, CED restricts coverage to within research studies. Coverage would not be available to any patients outside the study. We have considered options that would enroll beneficiaries initially into observational studies that could be used to assist in designing the appropriate randomized trial. However, the complexities of this option exceed the Agency's current ability to manage those vastly differing studies. In addition, as some of the data presented indicated, some patients do appear to have an improved QoL with appropriate ESA dosing. Thus, we will remove the proposed noncoverage from the final decision. However, since the tumor types for which these drugs are indicated are included below, the use of ESAs with these agents must meet the restrictions outlined below.

Proposed Noncovered Indication #11: Patients with treatment regimens including monoclonal/polyclonal antibodies directed against the epidermal growth factor (EGF) receptor

Public Comments
All commenters on this issue disagreed with noncoverage. However, many supported CED in lieu of noncoverage.

Additional Evidence
Specific evidence evaluating the addition of ESAs to chemotherapy regimens including these drugs was not available. Commenters presented data evaluating the differences in outcomes in patients in trials that included these drugs and found no differences in outcomes between those patients that received ESAs and those that did not.

FDA: This is a labeled indication.

The USP-DI does not list nor include any indication/discussion regarding treatment regimens including these drugs for either epoetin or darbepoetin alpha.

Response

The recognition of the epidermal growth factor receptor (EGFR) as an oncogene has resulted in the development of pharmacologic agents directed against the growth factor or its receptor. These agents have numerous targets including the external domain of the receptor, phosphorylation sites, and the DNA itself (anti-sense gene therapy) (Lai 2007; Paez 2004). These agents include cetuximab, erlotinib, gefitinib, and panitumumab. The signaling cascades for the epidermal growth factor and erythropoietin receptors are complex, but appear to have some overlap in pathways or targets (Oda 2005; Witthun 1993). For example, STAT-3 activation appears to occur with both (Grandis 1998; Kirito 2002). This overlap suggests that the efficacy of anti-EGFR therapy could be diminished by concomitant ESA use. Definitive answers are not available as prospective drug interaction studies have not been performed. The recent termination of the PAACE trial which assessed chemotherapy with avastin +/- panitumumab for decreased survival and pulmonary thrombosis in the experimental treatment arm suggests that these interactions cannot be predicted (Amgen press release).

Summary
Some evidence supports the pathophysiologic construct that ESAs can stimulate certain growth factors (VEGF, EGFR) that are the targets of chemotherapy. The appropriate evidence would be randomized trials that evaluate the addition of ESAs to standard treatment regimens. That evidence is not available. We have strongly considered, as many commenters suggested, whether this indication would be appropriate for CED. However, CED restricts coverage to within research studies. Coverage would not be available to any patients outside the study. We have considered options that would enroll beneficiaries initially into observational studies that could be used to assist in designing the appropriate randomized trial. However, the complexities of this option exceed the Agency's current ability to manage those vastly differing studies. In addition, as some of the data presented indicated, some patients do appear to have an improved QoL with appropriate ESA dosing. Thus, we will remove the proposed noncoverage from the final decision. However, since the tumor types for which these drugs are indicated are included below, the use of ESAs with these agents must meet the restrictions outlined below.

Proposed Noncovered Indication #12: Anemia due to cancer treatment if patients have uncontrolled hypertension

Public Comments
All commenters on this issue supported the CMS proposed decision.

Additional Evidence
We received no additional evidence supporting the use of ESAs in cancer patients with uncontrolled hypertension.

FDA: Uncontrolled hypertension is a contraindicated use in both the Epogen (epoetin) and Aranesp (darbepoetin alpha) labels. We also note the following language in the labeling for Aranesp (darbepoetin alpha).

Patients with uncontrolled hypertension should not be treated with Aranesp (darbepoetin alpha); blood pressure should be controlled adequately before initiation of therapy. Blood pressure may rise during treatment of anemia with Aranesp (darbepoetin alpha) or epoetin. In Aranesp (darbepoetin alpha) clinical trials, approximately 40% of patients with chronic renal failure (CRF) required initiation or intensification of antihypertensive therapy during the early phase of treatment when the hemoglobin was increasing. Hypertensive encephalopathy and seizures have been observed in patients with CRF treated with Aranesp (darbepoetin alpha) or epoetin.

The USP-DI has similar language.

Response
Hypertension is a well-recognized complication of ESA therapy. Patients with uncontrolled hypertension are at greater risk of complications. The FDA label specifically lists this as a contraindication for ESA therapy.

Summary
The evidence reviewed and the comments received support the determination that ESAs are not reasonable and necessary in beneficiaries with cancer who have uncontrolled hypertension.

Proposed Noncovered Indication #13: Patients with thrombotic episodes related to malignancy

Public Comments
Some commenters agreed with CMS. However, some commenters suggested that with proper evaluation, certain patients might be successfully placed on ESAs and an anticoagulant and managed. Commenters noted that clinical guidelines include precautions about thrombotic adverse effects. Also, commenters expressed concern that there are many other potential causes of thrombotic events in cancer patients that may not be related to the malignancy.

Additional Evidence
We received no additional evidence on the use of ESAs in cancer patients with thrombotic episodes.

The FDA approved labeling for both Aranesp (darbepoetin alpha) and Procrit/Epogen (epoetin) lists the following:

Thrombotic and Cardiovascular Events
Overall, the incidence of thrombotic events was 6.2% for Aranesp (darbepoetin alpha) and 4.1 % for placebo. However, the following events were reported more frequently in Aranesp (darbepoetin alpha) -treated patients than in placebo controls: pulmonary embolism, thromboembolism, thrombosis, and thrombophlebitis (deep and/or superficial). In addition, edema of any type was more frequently reported in Aranesp (darbepoetin alpha)-treated patients (21%) than in patients who received placebo (10%).

Increased Mortality, Serious Cardiovascular and Thromboembolic Events
EPOGEN (epoetin) and other erythropoiesis-stimulating agents (ESAs) increased the risk for death and for serious cardiovascular events in controlled clinical trials when administered to target a hemoglobin of greater than 12 g/dL. There was an increased risk of serious arterial and venous thromboembolic events, including myocardial infarction, stroke, congestive heart failure, and hemodialysis graft occlusion. A rate of hemoglobin rise of greater than 1 g/dL over 2 weeks may also contribute to these risks.

To reduce cardiovascular risks, use the lowest dose of EPOGEN (epoetin) that will gradually increase the hemoglobin concentration to a level sufficient to avoid the need for red blood cell (RBC) transfusion. The hemoglobin concentration should not exceed 12 g/dL, the rate of hemoglobin increase should not exceed 1 g/d L in any two week period (see DOSAGE AND ADMINISTRATION).

The USP-DI has similar language.

Response
We remain concerned that ESAs may precipitate lethal thrombosis. However, thrombotic events may be unrelated to the episode of chemotherapy and unrelated to the use of ESAs. While we remain concerned about this potential adverse event, commenters clearly outlined the various regimens that are available to physicians in treating these episodes. Since it will not be clear in many cases that ESAs are the causative factor in thrombotic events, we are removing this restriction in coverage.

Summary
We have not included this proposed limitation in the final decision.

B. Indications covered with restrictions in proposed decision

Receptor Status in patients with cancer undergoing chemotherapy:

CMS proposed to use ESA receptor status of tumors as a selection criterion for those tumors that were more likely to have an adverse response to ESAs. While the data are preliminary, we believe that they do provide a plausible explanation for the tumor progression seen in the two trials.

Public Comments
Some commenters debated the relevance, the clinical significance, or even the existence of erythropoietin receptors on malignant or normal cells, and stated that CMS should not develop coverage criteria that are based on the putative role of these receptors in the development or progression of cancer or related conditions. Others criticized the currently available assays as being nonspecific. Others said that CMS should not extrapolate from basic science or *in vitro* studies in its discussion of a possible mechanism for the adverse outcomes associated with ESAs.

Additional Evidence
We have received no evidence or proposal for an alternative explanation for the tumor progression.

The FDA label and the USP-DI do not address the use of erythropoietin receptor status as a criterion for determining use of ESAs.

Response
We are aware that there is spirited discussion about erythropoietin receptors. We proposed a mechanism to explain the cancer progression that has been seen with the use of ESAs in clinical trials and which has been highlighted in the black box warning. Though various commenters have objected to our proposal, they have not offered alternative explanations.

The presence of erythropoietin receptors on nonmalignant cells does not exclude an effect of ESAs on malignant cells at physiologic or supraphysiologic levels. Similarly, erythropoietin may exert additional effects beyond its usual physiologic pathway.

Farrell and Lee have stated, "Given the potentially wide range of functions of erythropoietin and the erythropoietin receptor, the mechanisms underlying these functions must be determined. Interestingly, Lappin and colleagues, repeating some work done by Acs et al. found that erythropoietin receptors were present in tumor cells, but absent from surrounding normal breast tissue (Maxwell, unpublished data). This, Lappin noted, is significant because it suggests the potential use of erythropoietin receptors of a tumor to target an erythropoietin -attached drug to the tumor and not damage the surrounding healthy tissue (Farrell 2004).

Indeed, it is possible that erythropoietin as a ligand may be interacting with cells through other receptors as well as erythropoietin receptors. Regardless of the route, evidence of a biologic effect after exposure is paramount. Although some of the *in vitro* data are conflicting (Rosti 1993), these contradictions might be explained by the cell lines or tissues that were used. Erythropoietin might have its most important effects in certain tissue subsets. Indeed, Phillips et al. have recently shown that the stem cells that reside within a tissue are such an important subset (Phillips 2007). Breast cancer initiating cell (stem cells) exposed to erythropoietin increased both their population size and capacity for self-renewal.

Summary
We agree with the commenters on the lack of maturity of this data. However, in response to the commenters we will not use this distinction in the final policy. We will consider all solid tumor types, multiple myeloma, lymphoma, and lymphocytic leukemia, regardless of ESA receptor status, to fall under the restrictions defined below.

Proposed Restrictions

1. The hemoglobin/hematocrit levels immediately prior to initiation of dosing for the month should be < 9 g/dl (hematocrit < 27%) in patients without known cardiovascular disease and <10 g/dl/30% in patients with documented symptomatic ischemic disease that cannot be treated with blood. (We suggest that patients, especially those in the latter category, be alerted to the increased potential for thrombosis and sequelae.)

Public Comments
Many commenters stated that CMS arbitrarily selected the proposed maximum hemoglobin level at which ESA therapy could be initiated. Those who opposed this restriction suggested higher levels. ASH suggested that instead of identifying a hemoglobin level when ESA therapy is covered by Medicare, CMS should identify a level when the physician should evaluate the possible need for ESA therapy. Others commented that ESAs should be considered when the hemoglobin drops below 11 g/dL and should be stopped at a hemoglobin of 12 g/dL (hematocrit of 36%).

Additional Evidence
We received no additional published information regarding the threshold for intervention for transfusions/ESAs, the timing of anemia onset with chemotherapy and the rate of anemia onset with chemotherapy. Per Dr. Henry Chang, National Institutes of Health/National Heart/Lung Institute/Extramural (NIH-NHLBI-Extramural), there is a large on-going study that may address transfusion thresholds, albeit in a perioperative population.

The FDA label states that ESAs are indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy. ESAs are indicated to decrease the need for transfusions in patients who will be receiving chemotherapy. The dose should be titrated for each patient to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for blood transfusion and not to exceed 12 g/dL. Prior to the Black Box warning, some labels included a suggested hemoglobin target range of 10 -12 g/dL.

The USP-DI lists the treatment of anemia in adults with nonmyeloid malignancies in which the anemia is due to the effect of concomitantly administered chemotherapy in order to decrease the need for transfusion as an accepted indication. The General Dosing section includes the following language, "To reduce cardiovascular and thromboembolic risks, *the lowest dose of epoetin alfa should be used.* The dose administered should gradually increase the hemoglobin concentration to the lowest level sufficient to avoid the need for red blood cell transfusion. The hemoglobin concentration should not exceed 12 g per dL. However, in the Dose Adjustment/Therapeutic Goal section, the following language is included, "The dosage of epoetin must be individualized to maintain the hemoglobin within the suggested target range, 10 to 12 g per dL. At the physician's discretion, the suggested target hemoglobin range may be expanded to achieve maximal patient benefit."

For darbepoetin alpha, the following language is in 'General Dosing Information.'

To reduce cardiovascular risks, the lowest dose of darbepoetin alpha should be used. The dose administered should gradually increase the hemoglobin concentration to the lowest level sufficient to avoid the need for red blood cell transfusion. The hemoglobin concentration should not exceed 12g/dL.

ASCO and ASH guidelines recommended evaluating patients for the need for ESA therapy when the hemoglobin is at or below 10 g/dL.

Response
The current label for ESAs indicates that there is increased risk for death and serious cardiovascular events when the hemoglobin is greater than 12g/dL. The label does not identify a specific hemoglobin level for treatment initiation or treatment target in patients with anemia induced by chemotherapy. The goal is to avoid transfusions. Transfusions are not required for hemoglobin levels 10.0g/dL or greater. There are no definitive data regarding transfusion need, and by extension ESA need for patients with hemoglobin levels between 7 and 10 g/dL. We proposed that patients who have hemoglobin levels less than 9g/dL are potential candidates for initiation or continuation of ESA therapy. Many commenters recommended that we raise that to 11g/dL.

Removal of the hemoglobin target range of 10 – 12 g/dl indicates that treatment of chemotherapy induced anemia should no longer focus on keeping the hemoglobin above 10 g/dL but at the lowest level that will prevent transfusions while still remaining below 12 g/dL. Although transfusion guidelines no longer provide hemoglobin initiation levels, it is a common practice for physicians to only transfuse patients when the hemoglobin approaches or drops below 8 g/dL. Thus, use of ESAs should begin at a hemoglobin level most likely to prevent the hemoglobin from dropping to 8 g/dL.

The ODAC did not identify specific a hemoglobin target at which ESA therapy should begin, but recommended that FDA establish one.

We proposed that initiating ESAs at a hemoglobin of 9 g/dL would be a sufficient starting point to prevent transfusions. The commenters disagreed and recommended 11 g/dL but with the outcome of keeping the hemoglobin above 10 g/dL. They argued that ESAs may take several weeks to reach peak activity and that if not started earlier, the hemoglobin was likely to drop to transfusion levels. Evidence to support that was lacking.

Summary
Because changes in hemoglobin after chemotherapy do not appear to be precipitous and because a response to ESAs can be seen as early as 2 weeks, we do not believe that early intervention at a hemoglobin of 11 g/dL with ESAs is reasonable and necessary (Barrett-Lee 2000, 2006; Birgegard 2005, 2006, 2007; Coiffier 2001; Tas 2002). However, we do agree that a starting level of 9 g/dL has the potential to result in more hemoglobins dropping to transfusion levels and will thus modify our proposed decision and find that the use of ESAs is reasonable and necessary in beneficiaries with cancer undergoing myelosuppressive therapy when their hemoglobin levels immediately prior to initiation or maintenance of ESA treatment are < 10 g/dL (or the hematocrit < 30%).

2. The maximum covered treatment duration is 12 weeks/year.

Comment

Many commenters disagreed with the proposed overall 12-week limit on ESA coverage and noted that many chemotherapeutic regimens are longer than 12 weeks. Several commenters supported ESA therapy for 4 weeks to 12 weeks after cessation of myelosuppressive chemotherapy. Still others supported ongoing ESA therapy that could last for years. A commenter asked us to clarify the timeframe to distinguish anemia resulting from chemotherapy from anemia due to other causes. Some commenters suggested specific timeframes, such as six weeks, 90 days, and one year. Others were unclear if this meant a total of 12 weeks/year of 12 weeks after completion of chemotherapy.

Additional Evidence
No additional published data regarding the duration of anemia after myelosuppressive chemotherapy and the cessation of such therapies was presented except for studies describing residual post therapy tissue platinum levels (Stewart 1982, 1994; Tothill 1992; Vermorkem 1986). No additional substantive data discriminating between the anemia due to chemotherapy after cessation of therapy and the anemia of cancer were provided.

FDA and USP-DI do not address maximum doses in its recommended dosing.

Response
Our intent for this restriction was not clearly understood. The controlled segments of the registration trials were 12-16 weeks long. We do not have substantive information for longer treatment cycles and for repeat treatment cycles. There are limited data on the temporal aspects of marrow recovery and the duration of anemia after myelosuppressive chemotherapy (Barrett-Lee 2000, 2006; Birgegard 2005, 2006, 2007; Coiffier 2001; Tas 2002). The ODAC voted overwhelmingly (16-1) against the continuation of ESA therapy after the completion of chemotherapy, but did not define the time period beyond which persisting anemia could no longer be attributed to the chemotherapy. The public comments were varied. Thus, we have modified our initial proposal and have determined that treatment of anemia due to myelosuppressive chemotherapy is reasonable and necessary up to 8 weeks following the last dose of myelosuppressive chemotherapy.

Summary
We have determined that continued use of ESAs for beneficiaries with cancer whose anemia is related to chemotherapy is not reasonable and necessary after 8 weeks following the final dose of myelosuppressive chemotherapy in a chemotherapy regimen. There are no restrictions on chemotherapy regimen frequency or duration in this decision.

3. The maximum covered 4 week treatment dose is 126,000 units for erythropoietin and 630 µg for darbepoetin alpha.

Public Comments

Commenters on this topic generally opposed the maximum doses that we proposed. A commenter supported the implementation of maximum ESA dosage ranges, with the possibility for individual case consideration as an exception. Many felt that the other restrictions imposed would limit the overall dose. Some commented that the maximums were not therapeutically equal for the two drugs. Many recommended that we specify the starting and maintenance dose and not have a maximum dose. They questioned why CMS would impose dose limitations when the drug label does not.

Additional Evidence
No additional published information regarding the long term safety in cancer and cancer related conditions were provided. No additional published information comparing long term safety of ESAs for those who responded to low doses versus those who required high doses for any hemoglobin response versus non responders was provided.

The current FDA labels and USP-DI recommend a starting dose of 150U/kg/three times weekly for epoetin and 2.25 mcg/kg/week for darbepoetin alpha.

Response
We agree with the commenters that a fixed maximum covered dose may interfere with appropriate patient management. Labeled dosing is based upon weight and thus maximum doses will vary by weight. Although fixed dose studies have been conducted by the sponsors, are discussed in FDA labeling, and reported to be therapeutically equivalent, most of the labeled dosing is based on weight. Also, a more important issue is to begin at the lowest dose necessary to prevent transfusion. Thus, we will not continue with a fixed maximum dose limitation as imposed in the proposed decision, recognizing that the clinically appropriate number may vary with the beneficiary's weight and response to therapy. However, we will apply a limitation to the starting dose as indicated by the label. For epoetin, the recommended starting dose is no more than 150U/kg/TIW. For darbepoetin alpha, the recommended starting dose is no more than 2.25 mcg/kg/week. Maintenance of these doses may continue if the hemoglobin level has not risen about the initiation level of 10 g/dL (hematocrit 30%) 4 weeks after the initiation of treatment and the hemoglobin rise is ≥ 1 g/dL (hematocrit ≥ 3%).

Summary
We have determined that the starting dose for ESA treatment is the recommended FDA label starting dose, no more than 150 U/kg/three times weekly for epoetin and 2.25 mcg/kg/weekly for darbepoetin alpha. Equivalent doses may be given over other approved time periods. Maintenance of ESA therapy is the starting dose if the hemoglobin level remains below 10 g/dL (or hematocrit is < 30%) 4 weeks after initiation of therapy and the rise in hemoglobin is ≥ 1g/dL (hematocrit ≥ 3%).

4. Continued use of the drug is not reasonable and necessary if there is evidence of poor drug response (hemoglobin/hematocrit rise <1 g/dl/<3%) after 4 weeks of treatment.

Public Comment
Many commenters stated that non-response should result in the administration of a higher dose. Most recommended that at least one dose escalation be allowed to better identify non-responders. ASH suggested that ESAs should not be continued after eight weeks in the absence of response, assuming the appropriate dose increase has been attempted in low-responders. US Oncology supported discontinuation after six weeks if the hemoglobin did not rise 1 g/dl or greater. All commenters supported discontinuation of ESA therapy in the face of non-response. A few commenters proposed that no change in the hemoglobin level after ESA therapy was initiated, that is, no increase or decrease, should be accepted as evidence of response to ESA therapy.

Additional Evidence
No groups supplied published data on safety outcomes in poor responders. The change in transfusion need for poor responders after ESA dose increases is not well characterized because of the use of composite endpoints and the lack of stratification by response.

The FDA label recommends that epoetin be increased to 300U/kg/TIW if there is no rise in hemoglobin after 8 weeks. The label recommends that darbepoetin alpha dose be adjusted to prevent transfusions and keep Hgb < 12 g/dL.

Dosing recommendations listed in the USP-DI are confusing, and at times, contradictory. Under the "Three Times a Week Dosing,' it states, "If response is not satisfactory (no reduction in transfusion requirements or no rise in hemoglobin after 8 weeks), increase dose to 300 Units per kg of body weight three times a week to achieve the suggested target hemoglobin range, 10 to 12 g per dL. And, the 'Weekly Dosing' section states, "If after 4 weeks of therapy, the hemoglobin has not increased by 1 g per dL, in the absence of RBC transfusion, the epoetin dose should be increased to 60,000 Units weekly. If the patient has not responded after 4 weeks of additional therapy at 60,000 Units weekly, it is unlikely the patient will respond to higher doses of epoetin".

We note the following language in 'General Dosing Information (usual adult dose, anemia associated with chemotherapy in cancer patients)'

For patients receiving weekly administration, if there is less than a 1g/dL increase in hemoglobin after 6 weeks of therapy, the dose of darbepoetin alpha should be increased up to 4.5 mcg/kg of body weight.

Response

There is insufficient evidence to define specific regimens for treatment of nonresponders. However based upon the comments from the public, we are modifying this restriction to allow one dose escalation of 25% and increasing the total time period for assessment of response to 8 weeks. We will also clarify that the increase in dose shall only occur if the hemoglobin remains < 10g/dL (or the hematocrit < 30%).

Summary
We have determined that it is reasonable and necessary to increase the covered dose once by 25% in patients whose hemoglobin rise is < 1 g/dl (hematocrit rise < 3%) compared to pretreatment baseline over 4 weeks of treatment and the hemoglobin level has remained < 10 g/dL (hematocrit < 30%) after the 4 weeks of treatment. Continued use of the drug is not reasonable and necessary if the hemoglobin rise is < 1 g/dl (hematocrit rise <3 %) compared to pretreatment baseline after 8 weeks of treatment.

5. Continued administration of the drug is not reasonable and necessary if there is an increase in fluid retention or weight (5 kg) after 2 weeks of treatment.

Public Comments
We had very few commenters addressing this specific proposal. Of those who did, some commenters opposed this restriction citing lack of clinical evidence. Another comment suggested this be clarified to distinguish between fluid retention or weight gain not associated with cancer.

Additional Evidence
No additional data were submitted. The FDA approved labeling for both Aranesp (darbepoetin alpha) and Procrit/Epogen (epoetin) respectively reflect these concerns.

Thrombotic and Cardiovascular Events
Overall, the incidence of thrombotic events was 6.2% for Aranesp (darbepoetin alpha) and 4.1 % for placebo. However, the following events were reported more frequently in Aranesp (darbepoetin alpha)-treated patients than in placebo controls: pulmonary embolism, thromboembolism, thrombosis, and thrombophlebitis (deep and/or superficial). In addition, edema of any type was more frequently reported in Aranesp (darbepoetin alpha)-treated patients (21%) than in patients who received placebo (10%).

Increased Mortality, Serious Cardiovascular and Thromboembolic Events
EPOGEN (epoetin) and other erythropoiesis-stimulating agents (ESAs) increased the risk for death and for serious cardiovascular events in controlled clinical trials when administered to target a hemoglobin of greater than 12 g/dL. There was an increased risk of serious arterial and venous thromboembolic events, including myocardial infarction, stroke, congestive heart failure, and hemodialysis graft occlusion. A rate of hemoglobin rise of greater than 1 g/dL over 2 weeks may also contribute to these risks.

To reduce cardiovascular risks, use the lowest dose of EPOGEN (epoetin) that will gradually increase the hemoglobin concentration to a level sufficient to avoid the need for RBC transfusion. The hemoglobin concentration should not exceed 12 g/dL, the rate of hemoglobin increase should not exceed 1 g/d L in any two week period (see DOSAGE AND ADMINISTRATION).

The USP-DI has similar language.

Response
We remain concerned that ESAs may precipitate edema and heart failure. However, weight changes in cancer patents may have a multitude of causes. As discussed above in thrombotic events, it is typically not clear to practitioners that edema and heart failure would be due to the ESA versus other causes. Thus, we will not continue this restriction.

Summary
We are not including this proposed limitation in the final decision.

6. Continued administration of the drug is not reasonable and necessary if there is a rapid rise in hemoglobin/hematocrit >1 g/dl/>3% after 2 weeks of treatment.

Public Comments
Some public commenters suggested that the ESA dose be lowered rather than discontinuing ESA therapy. Others suggested that there was not enough clinical evidence to allow CMS to make this decision. Commenters cited the FDA label to decrease the dose, not discontinue ESA therapy.

Additional Evidence
No additional substantive published data were provided.

The FDA approved labeling as well as the USP-DI dosing recommendation for EPOGEN/Procrit (epoetin) and Aranesp (darbepoetin alpha) include the following:

If the hemoglobin increases by more than 1.0 g/dL in a 2-week period, the dose should be decreased by approximately 25%.

Response
In several clinical trials, patients with brisk hemoglobin responses were excluded from further dosing and follow-up. Brisk hemoglobin response has been linked to thrombosis.

Summary
We have determined that continued administration of the drug is not reasonable and necessary if there is a rapid rise in hemoglobin > 1 g/dl (hematocrit > 3%) in 2 weeks of treatment unless the hemoglobin remains below or subsequently falls to < 10 g/dL (or the hematocrit is < 30%) and there has been a dose reduction of 25% from the previously administered dose.

Summary of restrictions for covered indications:

For patients with anemia secondary to anticancer chemotherapy, ESAs are appropriate when the hemoglobin is < 10g/dL (hematocrit < 30%). The maximum dose for the first 4 weeks is 1800 U/kg for epoetin and 9 mcg/kg for darbepoetin alpha. If after the first 4 weeks the hemoglobin is > 10g/dL (hematocrit > 30%), ESA treatment is not covered. ESA treatment may resume if the hemoglobin again drops below 10g/dL (hematocrit below 30%). If after any 4 week ESA treatment cycle, the hemoglobin remains below 10 g/dL (hematocrit below 30%), ESA treatment may continue at the same dose. If after the first 4 week ESA treatment cycle, the hemoglobin rise is less than 1 g/dL (hematocrit < 3%) and the hemoglobin level remains < 10 g/dL (hematocrit < 30%), the dose may be increased by 25% one time. If the rise in hemoglobin is < 1g/dL (hematocrit < 3%) for 8 weeks in spite of a 25% increase in dose, ESA treatment should be discontinued. If after any 2 week period of time, the hemoglobin rise is > 1g/dL (hematocrit > 3%), then ESA treatment should be discontinued unless the hemoglobin is < 10 g/dL (hematocrit <3 0%) at which time ESA treatment may be reinstituted at a dose reduction of 25%. ESA treatment meeting the above requirements may be continued for 8 weeks following the completion of the final dose of myelosuppressive chemotherapy in a chemotherapy regimen.

IX. Conclusion

Emerging safety concerns (thrombosis, cardiovascular events, tumor progression, and reduced survival) derived from clinical trials in several cancer and non-cancer populations prompted CMS to review its coverage of erythropoiesis stimulating agents (ESAs). We reviewed a large volume of scientific literature, including basic science research, to see if these safety signals seen in randomized controlled trials could be reasonably explained in whole or in part by the actions of ESAs on normal or cancerous cells. In doing so we proposed conditions of coverage based on expression of erythropoietin receptors. The scientific understanding of this mechanism is a subject of continuing debate among stakeholders, continues to evolve, and can only be resolved through additional studies. We also reviewed a large volume of comments on the use of ESAs in myelodysplastic syndrome (MDS), a premalignant syndrome that transforms into acute myeloid leukemia (AML) in many patients. Though we continue to be interested in these specific issues, this final decision does not differentiate ESA coverage by the erythropoietin receptor status of the underlying disease, and we have narrowed the scope of this final decision to make no NCD at this time on the use of ESAs in MDS.

CMS has determined that there is sufficient evidence to conclude that erythropoiesis stimulating agent (ESA) treatment is not reasonable and necessary for beneficiaries with certain clinical conditions, either because of a deleterious effect of the ESA on their underlying disease or because the underlying disease increases their risk of adverse effects related to ESA use. These conditions include:

1. any anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis;
2. the anemia associated with the treatment of acute and chronic myelogenous leukemias (CML, AML), or erythroid cancers;
3. the anemia of cancer not related to cancer treatment;
4. any anemia associated only with radiotherapy;
5. prophylactic use to prevent chemotherapy-induced anemia;
6. prophylactic use to reduce tumor hypoxia;
7. patients with erythropoietin-type resistance due to neutralizing antibodies; and
8. anemia due to cancer treatment if patients have uncontrolled hypertension.

We have also determined that ESA treatment for anemia secondary to myelosuppressive anticancer chemotherapy in solid tumors, multiple myeloma, lymphoma and lymphocytic leukemia is only reasonable and necessary under the following specified conditions:

1. The hemoglobin level immediately prior to initiation or maintenance of ESA treatment is < 10 g/dL (or the hematocrit is < 30%).
2. The starting dose for ESA treatment is the recommended FDA label starting dose, no more than 150 U/kg/three times weekly for epoetin and 2.25 mcg/kg/weekly for darbepoetin alpha. Equivalent doses may be given over other approved time periods.
3. Maintenance of ESA therapy is the starting dose if the hemoglobin level remains below 10 g/dL (or hematocrit is < 30%) 4 weeks after initiation of therapy and the rise in hemoglobin is ≥ 1g/dL (hematocrit ≥ 3%).
4. For patients whose hemoglobin rises < 1 g/dl (hematocrit rise < 3%) compared to pretreatment baseline over 4 weeks of treatment and whose hemoglobin level remains < 10 g/dL after the 4 weeks of treatment (or the hematocrit is < 30%), the recommended FDA label starting dose may be increased once by 25%. Continued use of the drug is not reasonable and necessary if the hemoglobin rises < 1 g/dl (hematocrit rise < 3 %) compared to pretreatment baseline by 8 weeks of treatment.

5. Continued administration of the drug is not reasonable and necessary if there is a rapid rise in hemoglobin > 1 g/dl (hematocrit > 3%) over 2 weeks of treatment unless the hemoglobin remains below or subsequently falls to < 10 g/dL (or the hematocrit is < 30%). Continuation and reinstitution of ESA therapy must include a dose reduction of 25% from the previously administered dose.
6. ESA treatment duration for each course of chemotherapy includes the 8 weeks following the final dose of myelosuppressive chemotherapy in a chemotherapy regimen.

Local Medicare contractors may continue to make reasonable and necessary determinations on all uses of ESAs that are not determined by NCD.

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